REMARKS

The Applicants acknowledge the Office Action of October 29, 2008 with appreciation. The Examiner acknowledges the Response and Amendment of December 21, 2007, and the Applicants' election, with traverse, to prosecute the invention of Group I, including Claims 17-32 and 34-36, drawn to microcapsule compositions. Furthermore, the Office acknowledges the Applicants' election of the species perindopril tert-butylamine salt in response to the Office request for an election of species of perindopril active agent. The Office indicates that Claims 17-32 and 34-37 are pending in the application, of those, Claims 27, 29 and 31 are withdrawn from consideration as being drawn to a non-elected invention. Claims 17-26, 28, 30, 32 and 34-37 are presently under examination.

RESTRICTION REQUIREMENT/ELECTION OF SPECIES

With respect to the election of species which was also required by the Office, the Office states "the election of perindopril tert-butylamine salt **without traverse** is acknowledged." Thus, the Office states that Claims 27, 29, and 31 (directed to compositions comprising perindopril in the form of its arginine salt) have been withdrawn as being directed to a non-elected invention since there is no allowable generic or linking claim.

As you are aware, in our Response and Election, we stated the following:
The Applicants respectfully submit that the microcapsule composition comprising a perindopril active ingredient is the special technical feature which defines a contribution over the prior art, the subject matter of which the Office has not identified in the art. Based on this common technical feature, the Applicants respectfully submit that unity of invention exists. Thus, the Applicants ***traverse*** the Office conclusion that the application pertains to a plurality of patentably distinct inventions.

The Applicants note that the Office request for an election of species was based on its allegation of lack of unity of invention based on the Mesier, et al. reference. Moreover, as was stated in the provisional election and designation of species, such "election" was made in an attempt to advance the prosecution of the instant application "in the absence of success in traversing the restriction requirement", which traversal, if successful for the one, should apply to both. Thus, the Applicants request that the Office acknowledge the traversal of the election of species requirement, and request withdrawal of the finality of the election of species requirement. The Applicants also request rejoinder of the non-elected subject matter, Claims 27, 29 and 31, in accordance with MPEP § 821.04.

OBJECTION AS TO FORM:

The Office objects to the Abstract of the disclosure, quoting the preferred Abstract format.

The Applicants acknowledge the Office exposition of USPTO patent procedure (see MPEP § 608.01(b)), and the Office's objection as to the instant Abstract format. The Applicants note that the MPEP provides guidelines which are formulated to facilitate the rapid and uniform prosecution of applications. The Applicants have considered the Office suggestions regarding the Abstract format and submit that they will, in the future, strive to conform to the non-statutory preferences.

The Office objects to Claim 1, actually Claim 17, as to form, in particular for the term "reservoir" in quotes.

With the instant Response and Amendment, the Applicants amend Claim 17 in accord with the Office request to delete the quotation marks. Withdrawal of the objection as to form of Claim 17 is respectfully requested.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH:

The Office rejects Claim 22, actually Claim 37, under 35 U.S.C. § 112, second paragraph, for failing to claim with particularity. It is the position of the Office that the phrase "including a human" represents a subgeneric phrase within a generic phrase and that, therefore, the scope of the claim is unclear.

With the instant Response and Amendment, Claim 37 is amended to delete the phrase "including a human" from Claim 37. Furthermore, the Applicants add new Claim 38, which depends from Claim 37, and which is directed to the claimed method wherein the living animal body is a human. Support for new Claim 38 may be found in former Claim 37.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

OBVIOUSNESS UNDER 35 U.S.C. § 103:

Claims 17-26, 28, 30, 32, and 34-37 are rejected for obviousness under 35 USC § 103(a) based on the disclosure of Garthwaite, et al. (US Published Application No. 2002/0132001) in view of Guez, et al. (US Patent No. 6,653,336).

It is the position of the Office that Garthwaite, et al. teach a composition comprising dual antihypertensive agents wherein the first agent is eplerenone and the second agent is preferably a different antihypertensive agent such as a diuretic or an ACE inhibitor. The Office notes that the composition is further taught as a capsule comprising enterically coated pellets. The Office acknowledges that Garthwaite, et al. do not expressly teach microcapsules comprising the elected t-butylamine salt of perindopril or a combination of microcapsules comprising perindopril t-butylamine and microcapsules comprising indapamide.

It is the position of the Office that Guez, et al. disclose orally administering a combination dosage form comprising an ACE inhibitor and a diuretic for the treatment of arteriolo-capillary microcirculatory disorders such as arterial hypertension, and that the reference further discloses that the preferred combination

is perindopril t-butylamine and indapamide. Furthermore, the Office finds that Examples 1 and 2 teach tablet formulations comprising perindopril t-butylamine and indapamide in combination with hydrophobic polymeric lubricants such as magnesium stearate and hydrophilic polymeric cellulose compounds such as microcrystalline cellulose. The Office acknowledges that Guez, et al. do not expressly teach the two preferred active ingredients (i.e., perindopril t-butyl amine and indapamide) in the form of microencapsulated pellets or granules nor does the reference expressly teach compositions wherein the two active ingredients are encapsulated separately from one another but contained in the same dosage form.

Thus, the Office concludes that, in view of the combined teachings of Garthwaite, et al. and Guez, et al., it would have been obvious to one skilled in the art to prepare a composition comprising hydrophilic/hydrophobic polymer encapsulated perindopril and indapamide particles to arrive at the instantly claimed invention.

The Applicants submit that Garthwaite, et al. may disclose delayed release compositions comprising an aldosterone antagonist, which aldosterone antagonist may be combined with other antihypertensive agents; however, the reference does not teach a composition comprising an aldosterone antagonist in combination with an ACE inhibitor, specifically, let alone compositions comprising both active ingredients in a reservoir microcapsule dosage form for the delayed-release and controlled-release of a drug active. Moreover, the Office acknowledges that, "Garthwaite, et al. do not expressly teach the microcapsules as comprising the elected tert-butylamine salt of perindopril or the claimed combination of said salt microcapsules with indapamide microcapsules." (See page 8 of the instant Office Action).

What is more, the Office acknowledges that, "Guez, et al. do not expressly teach the two preferred active ingredients in the form of microencapsulated pellets or granules nor are the two actives expressly taught as being encapsulated separate from one another but within the same dosage form." (See page 9 of the instant Office Action).

It is well-settled that to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

The Applicants submit that the Office has not demonstrated that Garthwaite, et al. and Guez, et al. teach or suggest the limitations of the instant claims drawn to reservoir microcapsule compositions for delayed and controlled release of perindopril. Moreover, as discussed above, the Office acknowledges that the cited art do not teach microcapsules comprising tert-butylamine salt of perindopril or the claimed combination of said salt microcapsules with indapamide microcapsules.

The instant generic Claim 17 is drawn to reservoir microcapsule compositions for the delayed and controlled release of perindopril or a pharmaceutically acceptable salt thereof, for oral administration.

The generic claim defines the microparticles of perindopril, or a pharmaceutically acceptable salt thereof, to be each covered by a coating film, the coating film being formed from a composite material of a hydrophilic polymer A carrying groups ionized at neutral pH, and a hydrophobic compound B, which is less than 40% by weight of the total mass of the microparticle. The instant claims define the hydrophilic polymer A of the invention to be selected from cellulose compounds, copolymers of methacrylic acid and a methacrylic acid ester, copolymers of methacrylic acid and an acrylic acid ester and mixtures thereof. The instant claims define the hydrophobic compound B of the invention to be selected from vegetable waxes, hydrogenated vegetable oils, hydrogenated triglycerides and mixtures thereof.

The Office finds that Guez, et al. disclose hydrophobic polymeric lubricants, such as magnesium stearate, and hydrophilic polymeric cellulose compounds, such as microcrystalline cellulose.

The Office, therefore, concludes that it would have been obvious to one of ordinary skill in the art to prepare a composition comprising hydrophilic/hydrophobic polymer

encapsulated perindopril as taught and suggested by Garthwaite, et al. and Guez, et al., and modify the ratio of the coating ingredients to produce the instant invention.

The Applicants submit that there is no support in law or fact for the Office position that it would have been obvious to prepare a microcapsule composition comprising hydrophilic/hydrophobic polymer encapsulated perindopril and routinely optimizing the ratio of the coating ingredients to provide delayed and controlled release of a drug active because only result effective variables can be optimized. A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimization or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

The cited art, Garthwaite, et al. and Guez, et al., do not teach or suggest a combination of a hydrophobic/hydrophilic polymer which is effective for providing both a delayed and controlled release profile for perindopril, nor do the cited art recognize that a combination of hydrophilic polymer A and hydrophobic compound B may provide both delayed release and controlled release of a drug active, and therefore, the combination may not be optimized for such a release profile.

The Applicants submit that the Office has not identified a suggestion or motivation to modify the ratio of the coating ingredients to produce the instant reservoir microcapsule compositions for the delayed and controlled release of perindopril. Therefore, the Office basis for finding obviousness, that it would be obvious to modify the ratio of the coating ingredients to produce the instant invention, cannot be sustained by perfunctory statements and speculation.

As taught in the instant specification at pages 8 and 11, the instant galenic forms provide delayed and controlled release of perindopril, or a pharmaceutically acceptable salt thereof, by means of a dual triggering mechanism, "time dependent" release, triggered at the end of a controlled time in the stomach, and "pH dependent" release, triggered by an increase in pH when the galenic form passes into the intestine.

The specification, at page 2, teaches that the reservoir microcapsule compositions of the instant invention are administrable once per day, guaranteeing the release and absorption of the active ingredient at the desired moment and allowing arterial hypertension to be controlled effectively over the entire day and in the morning, an advance over existing immediate release formulations of perindopril.

Garthwaite, et al. teach delayed release of an aldosterone antagonist, which drug release is coincident with aldosterone synthesis (paragraph [0020]), and which formulations allow for the release of only a minimal amount of aldosterone antagonist in the first 4 to about 12 hours after ingestion (paragraph [0055]). Garthwaite, et al. further teach that following this delay period, the formulation released the majority of the drug relatively quickly, e.g., within 1-3 hours (see paragraph [0057]). Thus, Garthwaite, et al. are silent with respect to delayed and controlled release of an aldosterone antagonist.

Furthermore, the Applicants submit that Guez, et al. do not supplant the Garthwaite, et al. deficiency of disclosure with regard to delayed and controlled release of a drug active. Guez, et al. teach that the corresponding pharmaceutical compositions are those which allow the instantaneous or delayed release of the active principles. (See Column 3, lines 47-50). Guez, et al. are silent with respect to controlled release of a drug active.

Consequently, the Examiner's conclusory assertions regarding the obviousness of the instant reservoir microcapsule compositions for delayed and controlled release, are not supported by the art of record.

Furthermore, the Applicants demonstrate material differences in the instant compositions over the delayed release formulations taught in Garthwaite, et al., distinguishing the instant reservoir microcapsule compositions for the fact that microcapsule compositions exhibit delayed and controlled release performance characteristics.

Garthwaite, et al., in Figure 1, disclose a profile of the blood serum concentration of an aldosterone antagonist after ingestion of such aldosterone antagonist of the delayed release formulation. The data demonstrate a delayed release of the aldosterone antagonist after an extended lag time and no controlled release period. Moreover, with regard to the absence of a controlled release period, Garthwaite, et al. teach that the formulation releases the majority of the drug relatively quickly, within 1-3 hours (paragraph [0057]).

The Applicants provide additional evidence which demonstrate the properties of the instant reservoir microcapsule compositions which exhibit both delayed-response and controlled-response performance characteristics for perindopril. This evidence is provided in the form of a Declaration under 37 CFR § 1.132 executed by Dr. Patrick WÜTHRICH. As is set forth in the declaration, Dr. Patrick WÜTHRICH is Director of Pharmaceutical Development at LES LABORATOIRES SERVIER.

As stated by Dr. Patrick WÜTHRICH, the oral pharmaceutical forms of the present patent application are used in the treatment of arterial hypertension and heart failure and have demonstrated original activity in pharmacokinetic trials. Dr. Patrick WÜTHRICH provides pharmacokinetic data which demonstrates *in vivo* blood level concentrations of perindopril, which perindopril is covered by at least one coating film comprising at least one hydrophilic polymer A and at least one hydrophobic compound B according to the instant invention.

Dr. Patrick WÜTHRICH states that a latent period of about 4 hours is observed wherein the active principle, perindopril, is not released in the plasma and said latent period is followed by a controlled-release period of about 12 hours.

Furthermore, Dr. Patrick WÜTHRICH states that a latent period of about 8 hours is observed wherein the active principle, perindoprilat (active compound liberated *in vivo* by enzyme action), is not released in the plasma and said latent period is followed by a controlled-release period of about 14-16 hours.

In sum, the Applicants demonstrate that the instant galenic form allows perindopril, or a pharmaceutically acceptable salt thereof, to be released with a delayed release profile that has a latent period (1 to 8 hours) followed by a controlled release phase (12 to 16 hours), and which release profile the Applicants demonstrate to be different from the release profile taught in the cited art.

The Applicants submit that the cited art, Garthwaite, et al. and Guez, et al. do not teach or suggest the instant reservoir microcapsule compositions for delayed and controlled release of perindopril. Moreover, the Applicants have demonstrated that the instantly claimed microcapsule compositions exhibit delayed and controlled response performance characteristics, which performance characteristics are not taught or suggested in the cited art. In view of the foregoing, the Applicants submit that the Office has failed to establish a factual basis for finding that the instant claims are obvious. Absent such showing, the Office has not met their burden to demonstrate that the rejected claims are *prima facie* obvious.

In view of the arguments presented, and the Declaration of Dr. Patrick WÜTHRICH, withdrawal of the rejection under 35 U.S.C. § 103(a) and expeditious passage of the application to issue is respectfully solicited.

* * * * *

Accordingly, entry of the present Response and Amendment, and Declaration, reconsideration and withdrawal of the previous Election of Species Requirement and/or rejoinder of Claims 27, 29 and 31, and reconsideration and withdrawal of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

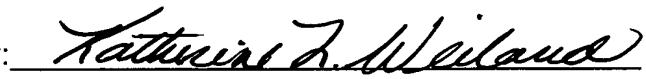
It should be apparent that the undersigned agent has made an earnest effort to place this application into condition for immediate allowance. If she can be of assistance to the Examiner in the elimination of any possibly-outstanding

insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call her at the below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

By: 

KATHERINE L. WEILAND

Dated: April 27, 2009
Customer No.: 25,666
Seventh Floor, Kalamazoo Building
107 West Michigan Avenue
Kalamazoo, MI 49007
(269) 382-0030

Enclosure: Extension of Time, three (3) months, under 37 CFR § 1.17(a)(3) and Fee in the form of a check in the amount of $1,110.00; Listing of Claims; Executed Declaration under 37 CFR § 1.132 and accompanying *Curriculum Vitae* of Dr. Patrick WÜTHRICH; and Postal Card Receipt.

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THE COMMISSIONER IS HEREBY AUTHORIZED TO CHARGE ANY FURTHER OR ADDITIONAL FEES WHICH MAY BE REQUIRED (DUE TO OMISSION, DEFICIENCY, OR OTHERWISE), OR TO CREDIT ANY OVERPAYMENT, TO DEPOSIT ACCOUNT NO. 08,3220.